administered to reduce the drug's cost, remains to be determined. This case demonstrates that a short-term regimen of erythropoietin and iron supplementation may allow high-dose chemotherapy to be offered to those individuals unwilling to accept blood products.

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Chronic Lymphocytic Leukemia Supervening in Non-Hodgkin's Lymphoma (Diffuse, Mixed-Cell Type)

To the Editor: Several reports have documented patients exhibiting different histologic subtypes of non-Hodgkin's lymphoma (NHL) in multiple sites (discordant lymphoma), or in a single tumor mass (composite lymphoma) [1,2]. However, few authors have clarified whether such lymphomas presenting with divergent histologic subtypes arise from a original common clone or from distinct malignant clones [3]. Related phenomena have been observed in Richter's syndrome, in which large-cell lymphoma supervenes in patients with chronic lymphocytic leukemia (CLL). Several authors have reported on immunophenotypic and immunogenotypic analyses regarding the clonal relationship between CLL and large-cell lymphoma, and it is generally considered that two morphologically distinct neoplasms were evoluted from the same clone [4,5]. Our case of CLL arising in a patient with long-standing NHL (diffuse, mixed-cell type) showed the reverse pattern, in which the lowgrade component supervened in the course of high-grade lymphoma. We examined the clonal relationship of these two malignancies by a combination of immunophenotypic and immunogenotypic analysis.

In October 1988, a 62-year-old man had general lymphadenopathy. He had diffuse lymphadenopathy up to 2 cm in the cervical, axillary, and inguinal regions, but no hepatosplenomegaly. At that time, results of a blood workup were as follows: hemoglobin level, 14.7 g/dl; leukocyte count, 9,200/μl (neutrophils 62%, lymphocytes 27%); and platelet count, $21.9 \times 10^4/\mu l$. An abdominal computed tomographic scan and gallium scan revealed diffuse lymphadenopathy in the cervical, axillary, inguinal, and periaortic regions. Rt-cervical lymph node biopsy showed NHL (diffuse, mixed-cell type). Immunophenotypic analysis of lymph-node cell suspensions showed a preponderance of CD5(−), CD19(+), CD20(+), and surface Ig(−) cells. Bone-marrow aspiration was normal. He was admitted to hospital and treated with combined chemotherapy (vincristin, cyclophosphamide, prednisone, and doxorubicin), resulting in partial remission.

Although an abdominal computed tomographic scan after chemotherapy revealed residual lymphadenopathy in the periaortic regions, surface lymph

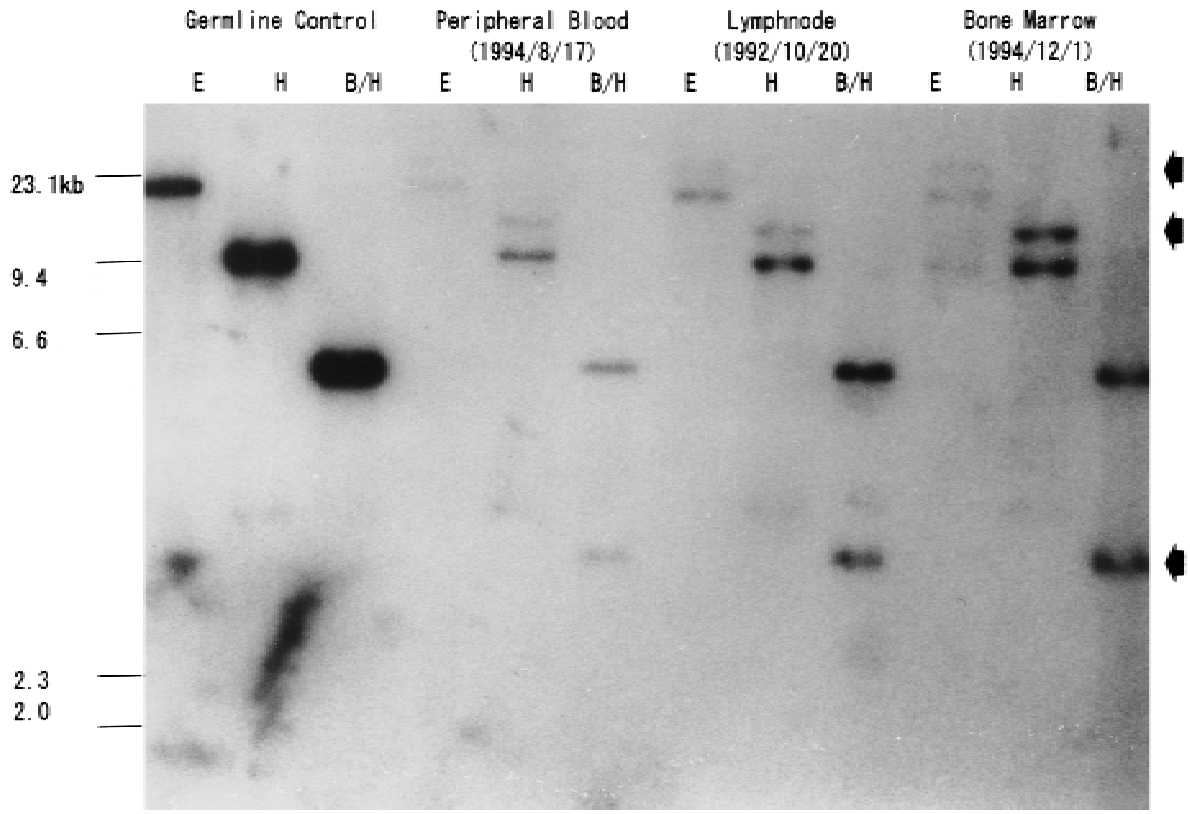

Fig. 1. Immunoglobulin (Ig) gene rearrangement analysis of DNA from lymph node (October 1992), peripheral blood cells (August 1994), and bone marrow (December 1994), using a probe to the joining region of the Ig heavy-chain gene (J_H). DNAs were digested with *Eco*RI (E), *Hind*III (H), and *Bam*HI/*Hind*III (B/H) restriction enzymes. Arrows indicate rearranged bands.

nodes decreased in size and became impalpable. After discharge in February 1989, he was treated with maintenance chemotherapy every 3 months for 2½ years. In October 1992, he had lt-inguinal lymph-node swelling and lymphocytosis. His leukocyte count was 10,000/μl (neutrophils 23%, lymphocytes 72%), hemoglobin level of 10.2 g/dl, and platelet count of $9.2 \times 10^4/\mu l$. The peripheral blood and bone marrow were infiltrated by small to medium-sized lymphoid cells. Immunophenotypic analysis of the lymphoid cells showed a preponderance of CD5(+), CD19(+), CD20(+), and surface Ig(−) cells. In contrast, lt-cervical lymph-node biopsy showed NHL (diffuse, mixed-cell type). He was admitted to hospital and treated with remission-induction chemotherapy (cytosine arabinoside, aclarubicin, and methyl prednisolone). Lt-inguinal lymph-node swelling disappeared, but lymphocytosis continued. In May 1994, his leukocyte count increased to 17,100/μl (neutrophils 20%, lymphocytes 73%), and low-dose etoposide (25 mg/day) as started. This was continued intermittently until October 1995, when swelling of the lt-inguinal lymph node and interstitial pneumonia developed. Lt-inguinal lymph-node biopsy revealed the proliferation of small lymphoid cells, which were compatible with the pathological features of CLL. The patient died of respiratory failure on November 29, 1995.

Sequential immunogenotypic analysis was performed on lymphoid cells obtained from the lymph node (October 1992), peripheral blood (August 1994), and bone marrow (December 1994). DNA from these materials showed identical rearrangements with a J_H gene probe (Fig. 1). Analysis with kappa, lambda, and TCR-β gene probes showed germline configuration.

In conclusion, the pathological and immunophenotypic analysis suggested that the patient had discordant lymphoma which consisted of CD5(−) NHL and CD5(+) CLL. The identical immunoglobulin gene rearrangement provided evidence for the evolution of two morphologically distinct neoplasms from the same clone.

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Thromboembolic complication of splenectomy in unstable hemoglobin disorders: Hb Olmsted, Hb Köln

To the Editor: We read with interest the article by Thuret et al. [1] in the February 1996 issue concerning ''Priapism Following Splenectomy in an Unstable Hemoglobin: Hemoglobin Olmsted . . .''

We share the authors' view that severe thromboembolic complications may follow splenectomy in patients who have severe chronic hemolytic disease, particularly in those cases that remain severely anemic following splenectomy. However, their statement that the original case of hemoglobin Olmsted hemolytic anemia died at age 37 of pulmonary infarction is not correct. The authors appear to have confused our case of hemoglobin Olmsted disease with the case of fatal pulmonary infarction in a patient with hemoglobin Köln disease who had been splenectomized, reported by Egan and Fairbanks [2]. We concur with the authors' observation that the isopropanol test is negative for unstable hemoglobin in specimens containing hemoglobin Olmsted, but that commonly used heat tests for hemoglobin instability are strongly positive. In screening for unstable hemoglobins, both tests must be used.

This letter permits us the opportunity to provide the final note concerning the original case of hemoglobin Olmsted hemolytic anemia [3]. The patient continued to have severe hemolytic anemia, with venous blood hemoglobin concentration usually in the range of 60–80 g/l. Transfusions were required periodically. At age 36 he experienced acute severe hepatic and renal failure, with serum bilirubin concentration in excess of 30 mg/dl (>500 μmol/l), and he died. During this terminal interval, he also had a severe hemorrhagic diathesis that appeared to be due to disseminated intravascular coagulation. Whether this coagulopathy contributed to hepatic and renal failure is uncertain, as postmortem examination was declined by his family.

Apparently, both our case and the Marseille case of Thuret et al. represented de novo mutations. The case in Marseille may now be the only known surviving case of hemoglobin Olmsted hemolytic anemia.

As regards the effect of splenectomy in hemoglobin Köln disease, although we have advised against it, splenectomy has nonetheless been performed in about half the cases known in four Minnesota families with this disorder. We are unaware of any other cases that have manifested either erythrocytosis or thromboembolic complications following splenectomy. The anemia does not appear to be ameliorated, but it is usually very mild or completely compensated before splenectomy. Patients seem generally to be about as well after splenectomy as before.

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Type III Hypersensitivity Reaction With the Use of Interferon-α

To the Editor: Interferon-α (IFN-α), produced by recombinant DNA technology, is in clinical use for the treatment of hematologic malignancies such as chronic myelogenous leukemia (CML), as well as other malignant and nonmalignant conditions [1]. Side effects described with the use of IFN include a flu-like syndrome, as well as gastrointestinal, central nervous system, and hematologic toxicities. There is evidence that IFNs may enhance pre-existing autoimmune disorders or induce their occurrence [1]. This report describes a case of type III hypersensitivity, an uncommon side effect, in a patient with CML treated with IFN-α.

A 50-year-old woman was diagnosed with Philadelphia chromosome positive (Ph+) CML in June 1991. She was treated with IFN-α 2b (Intron